

**AWARD NUMBER:** W81XWH-16-2-0067

**TITLE:** Extremity Regeneration of Soft Tissue Injury Using Growth Factor-Impregnated Gels

**PRINCIPAL INVESTIGATOR:** Simon Talbot, MD

**CONTRACTING ORGANIZATION:** Brigham and Women's Hospital Inc.  
Boston MA 02115

**REPORT DATE:** October 2017

**TYPE OF REPORT:** Annual

**PREPARED FOR:** U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

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<b>1. REPORT DATE</b> October 2017		<b>2. REPORT TYPE</b> Annual	
<b>4. TITLE AND SUBTITLE</b>  Extremity Regeneration of Soft Tissue Injury Using Growth Factor-Impregnated Gels		<b>3. DATES COVERED</b> 30 Sep 2016 - 29 Sep 2017	
		<b>5a. CONTRACT NUMBER</b>	
		<b>5b. GRANT NUMBER</b> W81XWH-16-2-0067	
<b>6. AUTHOR(S)</b> Simon Talbot, MD., Sarah Kinsley PA-C  E-Mail: <a href="mailto:sgtalbot@bwh.harvard.edu">sgtalbot@bwh.harvard.edu</a> ; <a href="mailto:skinsley@bwh.harvard.edu">skinsley@bwh.harvard.edu</a>		<b>5c. PROGRAM ELEMENT NUMBER</b>	
		<b>5d. PROJECT NUMBER</b>	
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		<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
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<b>13. SUPPLEMENTARY NOTES</b>			
<b>14. ABSTRACT</b> During this period, significant preliminary administrative approvals were obtained including IACUC and ACURO approvals. Given the complexity of these procedures this required repeated refinements. Four swine surgeries were performed, modifying the procedure after the first two and now with a successful and repeatable model. Ongoing studies to evaluate nerve and vessel regeneration continue to be tested. There has been ongoing research and development on the alginate gels and growth factors through collaboration with the Wyss Institute.			

**15. SUBJECT TERMS**

Nerve and vessel regeneration. Growth factor: VEGF and IGF.

**16. SECURITY CLASSIFICATION OF:****a. REPORT**

Unclassified

**b. ABSTRACT**

Unclassified

**c. THIS PAGE**

Unclassified

**17. LIMITATION  
OF ABSTRACT**

Unclassified

**18. NUMBER  
OF PAGES**

35

**19a. NAME OF RESPONSIBLE PERSON**  
USAMRMC**19b. TELEPHONE NUMBER** *(include area  
code)*

**Standard Form 298 (Rev. 8-98)**

Prescribed by ANSI Std. Z39.18

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**1. INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The overarching, long-term goal of this project is to develop technologies that maximize restoration of severely injured limbs by restoring muscle and nerve functions and avoiding amputation. This research specifically focuses on promoting regeneration of the injured host tissue by use of exogenous growth factors. A natural soft polymer gel material, alginate, has been fabricated to release two natural growth factors – vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1). Repeated injections of growth factor-alginate material are performed following a surgically induced traumatic ischemic injury and followed with muscle biopsies and nerve conduction studies to track regeneration. Preliminary results from small animal studies show that this approach can promote expansion of the host cells, and enhance restoration of blood flow, regeneration of muscle tissue, and reconnection of nerves. Currently, this project is being tested in a large animal swine model for its effectiveness in restoring blood flow, muscle and nerve tissue, and connection of nerve to muscles. The project will extend development of the injectable gel into a prototype product, suitable for commercialization.

**2. KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Vascularized endothelial growth factor (VEGF)  
Insulin-like growth factor-1 (IGF-1)  
Alginate gel  
Ischemia-reperfusion  
Large animal model

- 3. ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

**What were the major goals of the project?**

*List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.*

The major goals of this project as stated in the Statement of Work include:		
Specific Aim 1 – Evaluate alginate gel-based delivery of VEGF and IGF-1 in a large animal model of limb injury including ischemia-reperfusion and nerve.	Timeline in months per SOW	Completion
Milestone #1: Obtain IACUC and ACURO protocol approval	1-4	May 31, 2017
Milestone #2: Manufacturing process reduced alginate and testing methods established	8	July 17, 2017
Milestone #3: Successful large animal model and evaluation system	8	October 2, 2017
Milestone #4: Optimal ischemia time determined	12	75%

*For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.*

During this first year of study, accomplishments include development of a large animal study at USUHS, obtaining IACUC and ACURO approval at USUHS, developing the alginate manufacturing process and testing methods, and developing the histopathology processing of muscle biopsies.

The IACUC protocol underwent several revisions to determine the most ethical and appropriate treatment of swine during the surgical procedure and postoperatively. Four surgical procedures have been performed on swine to determine the optimal duration of ischemia to date. Two of the four swine were euthanized due to post-operative complications including skin necrosis and seroma development. The IACUC protocol was reevaluated and modified through multiple discussions with the USUHS veterinary and IACUC staff to optimize and develop a repeatable large animal protocol. Surgical changes include a smaller incision with improved skin closure and less muscle trauma, reducing the risk of infection, seroma and necrosis. Analgesia was modified to improve intra and post-operative pain management.

Under the modified protocol, two swine surgeries have been successfully performed. Ongoing studies to determine the optimal ischemia time are scheduled with plan to begin injecting gel based growth factor thereafter. Ongoing evaluation of regeneration within the large animal model is performed through muscle biopsies and EMG studies every 3 weeks through collaboration with USUHS and the Wyss Institute. The Wyss Institute has been instrumental in developing the protocol to process the muscle biopsies that is carried out by USUHS. The protocol is being optimized by the BWH Core Laboratory for staining motor endplates.

Through collaboration with the Wyss Institute, all processes to manufacture and test the alginate gel are being performed. This includes evaluation of oxidation, reduction, filtration, sterilization and reconstitution for production of the alginate gel. As the project continues, additional final product assessments will be carried out for cross linking density, sterility, endotoxin and growth factor release of the final product.

**What opportunities for training and professional development has the project provided?**

*If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.*

Nothing to report.



**How were the results disseminated to communities of interest?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.*

Nothing to report.

**What do you plan to do during the next reporting period to accomplish the goals?**

*If this is the final report, state “Nothing to Report.”*

*Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

During the next year, we will complete the studies to determine the optimal ischemia time and progress to determining the optimal dose-response relationship of various growth factors. This will be performed by injecting alginate based VEGF and IGF-1 using the established large animal model and determined ischemia time. Ongoing study of the alginate and growth factors will continue to be performed.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

**What was the impact on the development of the principal discipline(s) of the project?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).*

Development of the large animal model was based off prior small animal studies and a modified heterotopic swine hind-limb transplant model. Following euthanization of two swine, our large animal model was modified to reduce the traumatic burden on the animal limb without compromising induction of an ischemic-reperfusion injury. These surgical techniques including creation of smaller incisions, minimizing muscle injury and isolation of femoral vessels and sciatic nerve can be a proposed option for large animal hind-limb studies.

Overall, we expect this research to have significant impact with progression to commercialization of an injectable product to aid in muscle and nerve regeneration in traumatic injuries.

**What was the impact on other disciplines?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.*

Nothing to report.

**What was the impact on technology transfer?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:*

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

**What was the impact on society beyond science and technology?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:*

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

- 5. CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

**Changes in approach and reasons for change**

*Describe any changes in approach during the reporting period and reasons for these changes.*

*Remember that significant changes in objectives and scope require prior approval of the agency.*

Following the initial surgeries on two swine, both developed skin necrosis, seroma and infection at the surgical incision site ultimately resulting in euthanization. Through discussions with IACUC and veterinary staff, surgical technique and dissection approach was modified to include a smaller incision with limited traumatic burden, improved skin closure, and altered analgesia. These modifications reduced the risk of postoperative infection and skin necrosis and improved intra and postoperative pain control. These modifications did not compromise the integrity of the study as transection and repair of the vessels and nerves continues to be performed simulating the ischemia-reperfusion event in a traumatic limb. Following these modifications, two swine surgeries to date have been successfully performed with 4 additional surgeries planned before the end of 2018.

**Actual or anticipated problems or delays and actions or plans to resolve them**

*Describe problems or delays encountered during the reporting period and actions or plans to resolve them.*

A delay was incurred during the initial IACUC and ACURO approval process during the development of an acceptable large animal protocol. Following initiation of this protocol, a second delay ensued while we modified the surgical approach to minimize risk of infection, seroma development and skin necrosis. Following these modifications, IACUC approval was obtained. The surgical procedures have now resumed and have been successfully performed in a repeatable and reliable fashion. Procedures are scheduled in closer succession to eliminate lost time however completion of these studies will carry into our second year of study.

**Changes that had a significant impact on expenditures**

*Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

Nothing to report.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

*Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.*

**Significant changes in use or care of human subjects**

Nothing to report

**Significant changes in use or care of vertebrate animals.**

Following the initial surgeries on two swine, both developed skin necrosis, seroma and infection at the surgical incision site ultimately resulting in euthanization. Through discussions with IACUC and veterinary staff, surgical technique and dissection approach was modified to include a smaller incision with limited traumatic burden, improved skin closure, and altered analgesia. These modifications reduced the risk of postoperative infection and skin necrosis and improved intra and postoperative pain control. These modifications did not compromise the integrity of the study as transection and repair of the vessels and nerves continues to be performed simulating the ischemia-reperfusion event in a traumatic limb. Following these modifications, two swine surgeries to date have been successfully performed with 4 additional surgeries planned before the end of 2018.

**Significant changes in use of biohazards and/or select agents**

Nothing to report.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

**Journal publications.** *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

*dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

**Other publications, conference papers, and presentations.** *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (\*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**

*List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.*

Nothing to report.

- **Technologies or techniques**

*Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.*

Nothing to report.

- **Inventions, patent applications, and/or licenses**

*Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.*

- Nothing to report.

*Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:*

- *data or databases;*
- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

*Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change.”*

Name: Simon Talbot

Project Role: Principal Investigator

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1.20

Contribution to Project: Directs and oversees all phases of the study.

Name: EJ Caterson

Project Role: Co-Investigator

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 0.60

Contribution to Project: Assistance with planning and surgical aspects of the study.

Name: Sarah Kinsley

Project Role: Research Assistant

Research Identifier:

Nearest person month worked: 6.0

Contribution to Project: Involved in coordination and ensuring each phase of the project remains on schedule, writing protocols, purchasing.

Name: David Mooney

Project Role: Co-Principal Investigator

Research Identifier:

Nearest person month worked: 0.12

Contribution to Project: Involved in management of Wyss Institute input to project.

Name: Ed Doherty

Project Role: Co-Principal Investigator

Research Identifier:

Nearest person month worked: 1.20

Contribution to Project: Involved in coordination of production of Wyss gels.



Name: Alexander Stafford  
Project Role: Scientist  
Research Identifier:  
Nearest person month worked: 1.20  
Contribution to Project: Involved in production of gels.

Name: Des White  
Project Role: Research Associate  
Research Identifier:  
Nearest person month worked: 3.0  
Contribution to Project: Involved in production of gels.

Name: Tracy Snyder  
Project Role: Research Associate  
Research Identifier:  
Nearest person month worked: 6.0  
Contribution to Project: Involved in production of gels.

Name: Leon Nesti  
Project Role: Co-Principal Investigator  
Research Identifier:  
Nearest person month worked: 0.6  
Contribution to Project: Involved in management of USUHS staff and laboratory including coordination of animal experimentation on site.

Name: Amal Nadal  
Project Role: Research technician  
Research Identifier:  
Nearest person month worked: 6.0  
Contribution to Project: Involved in day-to-day running and local coordination of activities.

Name: Youngmi Ji  
Project Role: Staff scientist  
Research Identifier:  
Nearest person month worked: 3.0  
Contribution to Project: Involved in day-to-day running and local coordination of activities.

Name: Christian Walker  
Project Role: Program manager  
Research Identifier:  
Nearest person month worked: 0.6  
Contribution to Project: Involved in coordination of activities through USUHS.

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.*

Please see the attached and updated DoD support forms for Dr. Simon Talbot, Dr. Leon Nesti and Dr. Dave Mooney.

**Summary of changes for Dr. Dave Mooney:**

- Building the hematopoietic stem cell niche – Completed 2016
- iPSC-derived repair-responsive fibroblasts to heal diabetic foot ulcers – Completed 2016
- Biomaterial-based breast cancer vaccine – Completed 2016
- Hydrogels to promote tendon healing – Funding extended to 2018
- Human anti-MICA monoclonal antibodies for melanoma immunotherapy – Completed 2017
- Stimuli responsible, reloadable, drug eluting, smart hydrogels for graft targeted immunosuppression in vascularized composite Allotransplantation – Completed 2017

**Summary of changes for Dr. Simon Talbot:**

- A novel approach to lower extremity amputation to augment volitional motor control and restore proprioception – Active support July 2017 – June 2021
- Psychosocial predictors of VCA outcomes – Active support July 2017 – June 2020
- Engineering skeletal muscle with biodegradable hydrogels – Completed 2017

**Summary of changes for Dr. Leon Nesti:**

- Establishment of peripheral nerve injury data repository to monitor and support population health decisions – Active support October 2016 - September 2018
- Instructive biological scaffold for functional tissue regeneration following trauma to the extremities – Active support September 2012 – September 2017
- Dermal coverage of traumatic war wounds – Active support October 2012 – October 2017
- Development and characterization of in vivo models of explosive blast-related spinal column injury – Completed 2016
- Stem cell-based neurotrophic enhancements of an aligned nanofiber scaffold for nerve repair – Completed 2016

**What other organizations were involved as partners?**

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

*Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.*

*Provide the following information for each partnership:*

*Organization Name:*

*Location of Organization: (if foreign location list country)*

*Partner's contribution to the project (identify one or more)*

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

**Organization name:** United States Uniformed Health Services

**Location of Organization:** Associated with Walter Reed Military Medical Center in Bethesda, MD

**Partner's Contribution to the project:** Facilities and collaboration

**Organization name:** Wyss Institute for Biologically Inspired Engineering

**Location of Organization:** Associated with Harvard University. Located in Boston, MA

**Partner's Contribution to the project:** Collaboration and in-kind support developing the alginate and growth factor.

## 8. SPECIAL REPORTING REQUIREMENTS

**COLLABORATIVE AWARDS:** For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

**QUAD CHARTS:** If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

# Extremity Regeneration of Soft Tissue Injury Using Growth Factor Impregnated Gels

Log Number: DM153165

Award Number: W81XWH-16-2-0067

PI: Simon G. Talbot, MD

Org: Brigham and Women's Hospital

Award Amount: \$2.1 M



## Study/Product Aim(s)

Hypothesis: Injection of growth factor impregnated hydrogels can restore blood flow, promote muscle and nerve regeneration, and restore nerve connections to muscle.

• Aims: Evaluate biocompatibility and efficacy of alginate gel-based delivery of VEGF and IGF-1 in a large animal model of limb injury including ischemia-reperfusion and nerve transection-repair in support of future human clinical studies.

## Approach

Experiment 1: Determine optimal ischemia time and optimal growth factor dose in large animal model.

Experiment 2: Determine effect of VEGF and IGF-1 on nerve regeneration.

Experiment 3: Determine effect of VEGF and IGF-1 on ischemia-reperfusion.

## Timeline and Cost

Activities	2017	2018	2019
Determine optimal ischemia time and optimal growth factor dose in large animal model.			
Determine effect of VEGF and IGF-1 growth factor on nerve regeneration.			
Determine effect of VEGF and IGF-1 growth factor on ischemia-reperfusion.			
Estimated Budget (\$k)	733	702	665

Updated: 10/27/2017

L to R: Surgical incision site. Post-operative day one.



Accomplishment: Performed two surgeries in modified large animal model.

## Goals/Milestones

**CY17 Goal** – Determine optimal ischemia time and growth factor dose

☒ Develop large animal model

☒ Submit to IACUC and ACURO

☒ Begin experiment 1 on 20 animals

☒ Modify IACUC protocol to minimize postoperative risks

☒ Preliminary testing of alginate gel confirms consistency of product

☐ Complete experiment 1 – will overlap into year 2

**CY18 Goal** – Determine effect of growth factor on nerve regeneration

☐ Experiment 2 on 15 animals

☐ Experiment 3 on 15 animals

☐ Develop IND application to FDA

☐ Develop IND application to FDA

**Comments/Challenges/Issues/Concerns**

• Increasing number of surgeries to meet goal completion date

**Budget Expenditure to Date**

Projected Expenditure:

Actual Expenditure: \$490,069 (incl subcontracts \$182,701)

**9. APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

- DoD Support document for Simon Talbot
- DoD Support document for Leon Nesti
- DoD Support document for David Mooney

## Other Support, Simon Talbot

### Current

Title: *A novel approach to lower extremity amputation to augment volitional motor control and restore proprioception*

Time Commitment: 6.5% effort

Supporting Agency: US Department of Defense

Grants Officer: Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871

Performance Period: July 2017-June 2021

Level of funding: \$2,383,103

Project's Goals: The goal of this project is to develop and validate a new surgical technique to lower extremity amputation that incorporates agonist-antagonist myoneural interfaces

Specific aims:

1. To define a standardized approach to the performance of a novel operative procedure for both below knee (BKA) and above knee (AKA) amputations
2. To measure the degree of volitional motor activation and excursion achievable in the residual limb constructs, and to determine the optimal configuration and design of such constructs
3. To describe the extent of proprioceptive and other sensory feedback achievable through the employment of these modified surgical techniques
4. To validate the functional and somatosensory superiority of the proposed amputation technique over standard approaches to BKA and AKA
5. To develop a modified acute postoperative rehabilitation strategy suited to this new surgical approach

Overlap: This technology is equivalent but is based on upper rather than lower limbs.

Title: *Psychosocial predictors of VCA outcomes*

Time Commitment: 12.5% effort (PI)

Supporting Agency: US Department of Defense

Grants Officer: Sandra Rosario, USAMRAA, 843 Chandler St, Fort Detrick, MD 21740, (301) 619-4063

Performance Period: 07/1/2017-06/30/2020

Level of funding: \$563,380

Project's Goals: The goal of this project is to determine key factors in determining outcomes for VCA patients.

Specific aims

Specific Aim 1: To evaluate prospectively collected data on the International Registry of Hand and Composite Tissue Transplantation (demographics, medical/surgical factors) to determine variables associated with transplant 'success.' Specific Aim 2: To develop a model based on expert opinion, focusing on psychosocial parameters, to help objectify the psychosocial

evaluations of hand transplant patients. Specific Aim 3: To validate the model developed in Aims 1 and 2 in actual patients from the several large volume centers where complete data is available.

Overlap

None

Title: *Extremity regeneration of soft tissue injury using growth factor-impregnated gels (W81XWH-16-2-0067)*

Time Commitment: 10% effort

Supporting Agency: US Department of Defense

Grants Officer: Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871

Performance Period: 09/30/2016-09/29/2019

Level of funding: \$2,100,000

Project's Goals: The goal of this project is to investigate the use of growth-factor impregnated hydrogels for the improvement of nerve regeneration and limb function.

Specific aims: The specific aims of this grant are to determine if the use of injectable hydrogel combined VEGF and IGF-1 can improve nerve growth in a large animal model, and thereafter to determine dose, scheduling, and produce a product for FDA approval.

Overlap:

None

Title: *A novel protocol for upper extremity restoration by transplantation with intent for tolerance induction (W81XWH-12-2-0037)*

Time Commitment: 5% effort

Supporting Agency: US Department of Defense

Grants Officer: Elena G. Howell, DOD, 820 Chandler St, Fort Detrick, MD, 21702-5014, 301-619-6871

Performance Period: 09/30/2012-09/29/2017

Level of funding: \$ 2,005,315

Project's Goals: The goal of this project is to induce tolerance to upper extremity allografts in four human transplant recipients through a mixed chimerism approach.

Specific aims: (1) To perform upper extremity transplantation followed two months later by delayed bone marrow transplantation in four subjects; (2) To determine whether mixed lymphohematopoietic chimerism reduces the immune response to upper extremity allografts by in vitro analysis of recipient T- cell subtypes and function, allowing for reduction or withdrawal of immunosuppression after upper extremity/bone marrow transplantation; (3) To study the outcomes of upper extremity allotransplantation in a cohort of four patients for a period of one year post-transplant.

Overlap:

None

## **Previous**

Title: *Engineering skeletal muscle with biodegradable hydrogels (4R01DE013349-16)*

Time Commitment: 5% effort



Supporting Agency: National Institutes of Health  
 Grants Officer: Gabriel Hidalgo, NIDCR, 6705 Rockledge Drive, Bethesda, MD 20892-7986  
 Performance Period: 08/28/2014-06/30/2017  
 Level of funding: \$91,629  
 Project's Goals: The goal of this project is to test and further refine the use of biodegradable hydrogels in ischemia tissue and denervated tissue to improve tissue viability and recovery.  
 Specific aims: The aims are to examine the ability of alginate gel-based delivery of VEGF and IGF-1 to enhance engraftment and function of a denervated tibialis anterior muscle, in young and aged mice and in a rabbit gracilis muscle transfer model.  
 Overlap: Although the concept of tissue transfer and viability is central, there is no overlap between this animal model and the proposed clinical translational project.

Title: *Design and testing of a robotic system to perform microscale anastomosis (URAD)*  
 Time Commitment: 5% effort  
 Supporting Agency: The Charles Stark Draper Laboratory  
 Grants Officer: Mary Luther, Draper Laboratory, 555 Technology Square, Cambridge, MA 02139-3563, (617) 258-2361  
 Performance Period: July 2013-June 2014  
 Level of funding: \$110, 000  
 Project's Goals: The project goals were to develop micro-robotic technology for microsurgery.  
 Specific aims: The aims were to miniaturize and improve fidelity of micro-instruments through the development of micro-sensors and to modify existing robotic control systems for this purpose.  
 Overlap: None

### **Pending**

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## CURRENT / PENDING SUPPORT

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NAME LTC Leon J. Nesti, MD, PhD	POSITION TITLE Chief, Clinical and Experimental Orthopaedics, WRNMMC
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### CURRENT SUPPORT:

**Title:** Establishment of Peripheral Nerve Injury Data Repository to Monitor and Support Population Health Decisions

**Funding Agency:** MSIS/JPC-1

**Project Goal:** We propose to carry out epidemiologic chart reviews of approximately 400 patients with combat related peripheral nerve injuries who were referred to WRNMMC or SAMMC for tertiary care. A data registry will be established and algorithms developed to support health decisions.

**Specific Aims/Tasks:** Specific Aim 1. Establish a database registry of CR-PNI mechanisms, management and outcomes using both retrospective chart review and prospective patient enrollment. Specific Aim 2. Develop algorithms based upon evaluation of the CR-PNI registry to establish correlations between clinical history, management and outcomes in order to provide recommendations for clinical care that will improve outcome for peripheral nerve injury patients.

**Performance Period:** 10/1/2016 – 9/30/2018

**Level of Funding:** \$851,000

**Time Commitment:** 10%

**Funding Agency's Procuring Contracting/Grants Officer:** TBD

**Title:** Early Identification of Molecular Predictors of Heterotopic Ossification following Extremity Blast Injury: Animal Model Correlation with Human Disease

**Funding Agency:** CDMRP

**Project Goal:** The goal of this project is to explore the hypothesis is that the biologic processes that characterize heterotopic ossification in a blast amputation model in the Sprague-Dawley rat will closely resemble those observed in battle-injured soldiers. Correlation of animal and human HO findings will allow identification of common biomarkers that are present early in the process and are predictive of HO formation in wounded soldiers at greatest risk. These high-risk individuals would ultimately be enrolled in a clinical trial of therapeutic interventions known to effectively prevent HO in the civilian setting.

**Specific Aims/Tasks:** (1) To correlate gene- and protein- level expression related to osteogenesis in the animal model and human tissue. (2) To identify early-appearing gene- and protein-level expression in the animal model that predicts eventual development of human HO. (3) To validate early-appearing biomarkers to predict development of HO

**Performance Period:** 09/30/2013 – 09/29/2017

**Level of Funding:** \$434,497

**Time Commitment:** 10% effort

**Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:**  
Lisa Sawyer, U.S. Army Medical Research Acquisition Activity

820 Chandler Street, Fort Detrick, MD 21740-5014  
[Lisa.sawyer22.civ@mail.mil](mailto:Lisa.sawyer22.civ@mail.mil)

**Title:** Instructive Biologic Scaffold for Functional Tissue Regeneration Following Trauma to the Extremities

**Funding Agency:** CDMRP

**Project Goal:** The proposed clinical trial will establish the effectiveness of a UBMECM scaffold for the restoration of functional skeletal muscle tissue, including the restoration of blood supply and innervation. Successful completion of our objectives would provide a regenerative alternative to the current standard of care for extremity VML and restore quality of life to injured war fighters. We hypothesize that subjects who receive the UBM-ECM scaffold in the acute and subacute post-injury periods will have significant new muscle growth and improvements in strength in the treated extremity.

**Specific Aims/Tasks:** Specific Aim 1: To induce the de novo formation of at least 25% of the missing muscle tissue using UBM- ECM. Specific Aim 2: To restore at least 25% of the function of the involved muscle group.

**Funding:** \$1,487,923.08

**Performance Period:** 09/30/2012 – 09/29/2017

**Time commitments:** 10% Effort

**Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:**

Mirlene Desir, U.S. Army Medical Research Acquisition Activity Grant Specialist

820 Chandler Street, Fort Detrick, MD 21740-5014

T: 301-619-9656

[mirlene.desir.civ@mail.mil](mailto:mirlene.desir.civ@mail.mil)

**Title:** Dermal Coverage of Traumatic War Wounds

**Funding Agency:** CDMRP

**Project Goal:** The goal of the study described herein is to determine the effectiveness of the use of the ReCell device over a widened STSG mesh in combination with INTEGRA will improve upon the current standard of care.

**Specific Aims/ Tasks:** Specific Aim 1: Assess the preliminary effectiveness of ReCell treatment of full-thickness wounds treated with INTEGRA MBWM compared to a control site. Specific Aim 2: Assess the long-term effectiveness of ReCell treatment of full-thickness wounds treated with INTEGRA MBWM compared to a control site. Specific Aim 3: Evaluate safety of ReCell treatment of full-thickness wounds treated with Integra MBWM compared to control site.

**Performance Period:** 10/31/2012 – 10/30/2017

**Funding:** \$1,414,865

**Time Commitment:** 10% Effort

**Name and Address of Funding Agency's Procuring Contracting/Grants Officer:**

Sandra Rosario, U.S. Army Medical Research Acquisition Activity Grant Specialist - Gold Team

843 Chandler Street, Fort Detrick, MD 21740

T: 301-619-4063

[sandra.rosario@amedd.army.mil](mailto:sandra.rosario@amedd.army.mil)

**Title:** Clinical Evaluation of Decellularized Nerve Allograft with Autologous Bone Marrow Stem Cells to Improve Peripheral Nerve Repair and Functional Outcomes

**Funding Agency:** CDMRP

**Project Goal:** The proposed project is to conduct a phase I clinical safety evaluation of the synergistic effect of co treatments of a commercially available decellularized processed peripheral nerve allograft scaffold (Avance® Nerve Graft, AxoGen, Alachua FL) combined with autologous bone marrow stem cells (BMSC) for the reconstruction of mixed peripheral nerve gaps between 3 and 7 cm in length

**Specific Aims/Tasks:** Specific Aim 1 / Primary Outcome: Assess the safety profile of the processed nerve allograft when combined with autologous BMSC's as a treatment for reconstruction of mixed peripheral nerve gaps up to 70 mm. Specific Aim 2 / Secondary Outcome: Measure the efficacy of the processed nerve allograft when seeded with BMSC's and compare the outcomes to historical autograft and Avance® values by comparing the level of functional recovery. As well as compare other secondary efficacy endpoints such as: time to recovery, recovery to baseline, level and rate of reinnervation, quality of life, economic data and correlation of short and long term outcomes with regard to MESS and LSI scores

**Performance Period:** 07/01/2015 – 06/30/2018

**Funding:** \$2,325,412

**Time Commitment:** 10% effort

**Name and Address of Funding Agency's Procuring Contracting/Grants Officer:**

Sandra Rosario, U.S. Army Medical Research Acquisition Activity Grant Specialist - Gold Team  
843 Chandler Street, Fort Detrick, MD 21740

T: 301-619-4063

[sandra.rosario@amedd.army.mil](mailto:sandra.rosario@amedd.army.mil)

## **PREVIOUS SUPPORT:**

**Title:** Development and Characterization of in vivo Models of Explosive Blast-Related Spinal Column Injury

**Funding Agency:** DMRDP

**Project Goal:** To determine the influence of blast exposure on intervertebral disc's and muscle's molecular profile (gene expression on RNA level) on rat model.

**Specific Aims/Tasks:** Real-time PCR results (gene expression on transcription level) in blast and control rats IVD's and muscle at various time points.

**Performance Period:** 06/13/2014 – 04/30/2016

**Level of Funding:** \$396,800

**Time Commitment:** 10% effort

**Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:**

Steven Beck, USUHS

4301 Jones Bridge Road, Bethesda MD 20814

301-295-3970

[Steven.beck@usuhs.edu](mailto:Steven.beck@usuhs.edu)

**Title:** Stem Cell-Based Neurotrophic Enhancements of an Aligned Nanofiber Scaffold for Nerve Repair

**Funding Agency:** USAMRAA

**Project Goal:** To validate the efficacy of the MPC scaffold composite device in vivo using a rabbit model of nerve injury.

**Specific Aims/Tasks:** 1) To verify nanofibers alignment to the longitudinal axis of the device and determine the correlation between device density and distance between aligned fibers and to optimize the fabrication parameters for this device by determining range of fiber densities that will yield sufficient tensile and suture retention strengths that are necessary for surgical handling. 2) To determine whether the devices from Specific Aim 1 allow sufficient space between the aligned fibers for the migration of traumatized muscle-derived MPCs and microvascular endothelial cells through the device. 3) To verify that the axon scaffolding devices will support the neurotrophic functions of the MPCs and to validate the efficacy of the MPC scaffold composite device using an in vitro nerve regeneration model.

**Performance Period:** 9/1/2010-3/30/2016

**Level of Funding:** \$313,643

**Time Commitment:** 10% effort

**Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:**

Abigail Strock, U.S. Army Medical Research Acquisition Activity Grant Specialist - Gold Team  
843 Chandler Street, Fort Detrick, MD 21740

[301-619-2342](tel:301-619-2342)

[abigail.l.strock.civ@mail.mil](mailto:abigail.l.strock.civ@mail.mil)

**Title:** Virtual Stress Test of Healing Fractures

**Funding Agency:** USAMRAA

**Project Goal:** To identify Candidate BCT Clinical Endpoint. and compare the predictive performance of all the candidate BCT outcomes.

**Specific Aims/Tasks:** 1) To identify Candidate BCT Outcomes. Conduct a retrospective case-control clinical research study on 100 soldier patients with severe tibial fractures required external ring fixation, 50 of whom have had a significant clinical event (re-fracture, malunion, need for surgical revision) after resumption of full weight . 2) To identify the BCT-based Clinical Endpoint. Conduct a prospective observational clinical research study on 90 soldier patients with severe tibial fractures requiring external ring fixation. Using CT scans taken just prior to frame removal or resumption of full weight bearing, perform BCT analyses and compare the predictive performance of all the candidate BCT outcomes from Aim 1.

**Performance Period:** 9/30/2010-10/29/2013

**Level of Funding:**

**Time Commitment:** 10% effort

**Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:**

Jennifer Shankle, U.S. Army Medical Research Acquisition Activity Grant Specialist - Gold Team

843 Chandler Street, Fort Detrick, MD 21740

[jennifer.shankle@us.army.mil](mailto:jennifer.shankle@us.army.mil)

**PENDING SUPPORT:**

**Title:** Novel anti-fibrotic strategies in the targeted treatment and prevention of post-traumatic Heterotopic Ossification and enhancement of post-traumatic tissue regeneration.

**Funding Agency:** CDMRP

**Project Goal:** The proposed project is to research in-vitro and test in a small animal model a combination of Rapamycin and Proleukin as a novel treatment strategy to prevent the development of post-traumatic heterotopic ossification, reduce tissue fibrosis and promote normal tissue regeneration

**Specific Aims/Tasks:** Specific Aim 1: To determine the effectiveness of Rapamycin treatment in preventing fibrosis of muscle-derived MPCs in a cell culture system. Specific Aim 2: To assess the efficacy of Rapamycin-based therapy in preventing fibrosis and ectopic bone formation in an animal model. Specific Aim 3: Evaluate co-treatment with the immune modulator Proleukin to reduce an anticipated immunosuppression side effect of primary treatment.

**Performance Period:** 10/1/2016 – 9/30/2018

**Level of Funding:** \$499,664

**Time Commitment:** 5%

**Funding Agency's Procuring Contracting/Grants Officer:** TBD

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## CURRENT / PENDING SUPPORT

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NAME LTC Leon J. Nesti, MD, PhD	POSITION TITLE Chief, Clinical and Experimental Orthopaedics, WRNMMC
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**Level of Funding:** \$851,000

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**Level of Funding:** \$434,497

**Time Commitment:** 10% effort

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**Time commitments:** 10% Effort

**Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:**

Mirlene Desir, U.S. Army Medical Research Acquisition Activity Grant Specialist

820 Chandler Street, Fort Detrick, MD 21740-5014

T: 301-619-9656

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**Funding:** \$1,414,865

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T: 301-619-4063

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**Title:** Clinical Evaluation of Decellularized Nerve Allograft with Autologous Bone Marrow Stem Cells to Improve Peripheral Nerve Repair and Functional Outcomes

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**Performance Period:** 07/01/2015 – 06/30/2018

**Funding:** \$2,325,412

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## **PREVIOUS SUPPORT:**

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Steven Beck, USUHS

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**Title:** Stem Cell-Based Neurotrophic Enhancements of an Aligned Nanofiber Scaffold for Nerve Repair

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**Level of Funding:** \$313,643

**Time Commitment:** 10% effort

**Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:**

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**Title:** Virtual Stress Test of Healing Fractures

**Funding Agency:** USAMRAA

**Project Goal:** To identify Candidate BCT Clinical Endpoint. and compare the predictive performance of all the candidate BCT outcomes.

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**Level of Funding:**

**Time Commitment:** 10% effort

**Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:**

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843 Chandler Street, Fort Detrick, MD 21740

[jennifer.shankle@us.army.mil](mailto:jennifer.shankle@us.army.mil)

**PENDING SUPPORT:**

**Title:** Novel anti-fibrotic strategies in the targeted treatment and prevention of post-traumatic Heterotopic Ossification and enhancement of post-traumatic tissue regeneration.

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**Performance Period:** 10/1/2016 – 9/30/2018

**Level of Funding:** \$499,664

**Time Commitment:** 5%

**Funding Agency's Procuring Contracting/Grants Officer:** TBD